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## General synthesis of *P*-stereogenic compounds: the menthyl phosphinate approach†

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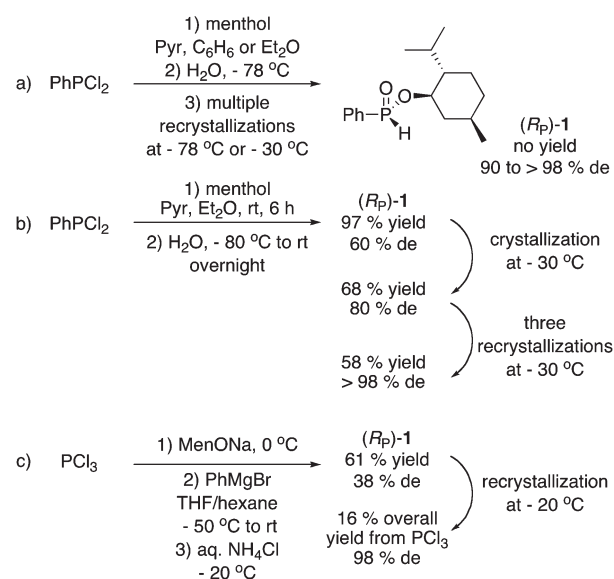
Easily prepared menthyl phosphinates of high diastereoisomeric purity provide versatile intermediates for the synthesis of *P*-stereogenic compounds. Previous efforts starting about fifty years ago have been hampered by a lack of generality so the menthyl route has been nearly abandoned. Herein we provide a general solution to this long-standing problem and describe a general synthesis of menthyl *H*-phosphinate and disubstituted phosphinate esters. The method to prepare these versatile precursors relies on a simple and inexpensive process avoiding the use of phosphorus trichloride, Grignard reagents, and complicated cryogenic crystallizations. Established protocols can then be employed to synthesize *P*-stereogenic secondary and tertiary phosphine oxides and therefore *P*-stereogenic phosphine ligands.

### Introduction

The synthesis of compounds featuring a chiral phosphorus atom (*P*-stereogenic compounds) has a long history dating as far back as the early twentieth century.<sup>1</sup> However, it was not until the 1960's that major progress was made in the field. Most notably, this is also when the use of phosphinate esters of naturally occurring *L*-(-)-menthol first appeared in the classic work of Mislow<sup>2</sup> and others.<sup>3</sup> The methodology was used by Knowles and coworkers for the synthesis of the bisphosphine ligand diPAMP in 1975.<sup>4</sup> Subsequent application of the ligand in the rhodium-catalyzed asymmetric hydrogenation of *L*-DOPA constitutes a milestone in asymmetric synthesis ultimately resulting in Knowles sharing the 2001 Nobel Prize in Chemistry with Noyori and Sharpless.

Since these pioneering contributions, numerous methods have been devised to prepare *P*-stereogenic compounds, and many excellent reviews have appeared on the subject.<sup>5</sup> Virtually all reactions available in the "asymmetric toolbox" have been employed for this purpose. Interestingly, menthyl phosphinates have largely fallen out of favor, in spite of their groundbreaking historical importance, and their well-established transformations into phosphine oxides (and ultimately phosphines). This situation is due to the fact that separating menthyl phosphinate diastereoisomers is often a very challenging task and each phosphinate requires different conditions.

The case of menthyl phenyl-*H*-phosphinate **1**, undoubtedly the most widely employed of the menthyl phosphinates to date, is illustrative (Scheme 1). In 1968, Emmick and Letsinger prepared **1** in 47% yield (from PhPCl<sub>2</sub>, pyridine, menthol then NaHCO<sub>3</sub>) but reported that the diastereoisomers could not be separated.<sup>3a</sup> Shortly thereafter, Farnham, Murray, and Mislow reported the preparation of **1** in 90% de after crystallization at -78 °C, but the yield was not reported (Scheme 1a).<sup>2b</sup> In 1995, Hammer and coworkers separated the mixture using a chiral HPLC column, once again without a yield being reported.<sup>6</sup> Han and coworkers then employed (*R<sub>P</sub>*)-**1** in a series of pub-



**Scheme 1** Literature preparations of menthyl phenyl-*H*-phosphinate (*R<sub>P</sub>*)-**1**.

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† Electronic supplementary information (ESI) available: Detailed experimental procedures and spectral data, <sup>1</sup>H-, <sup>13</sup>C-, <sup>31</sup>P-NMR, and HRMS (PDF). See DOI: 10.1039/c6ob01413e



lications,<sup>7</sup> but the yield was never reported. Ultimately in 2015, they published a detailed experimental procedure for the improved synthesis of (*R<sub>P</sub>*)-**1** *via* low temperature hydrolysis of PhP(OMe)Cl, resulting in a 57% yield and >98% de after three recrystallizations at -30 °C (Scheme 1b).<sup>8</sup> In 2011, Gati-neau, Giordano, and Buono reported a detailed preparation of (*R<sub>P</sub>*)-**1** using MenOPCl<sub>2</sub> and PhMgCl, in 16% overall yield and 98% de after two recrystallizations at -20 °C (Scheme 1c).<sup>9</sup> These authors also prepared *o*-tolyl and 1-naphthyl derivatives in comparable yields.<sup>9</sup>

As can be seen in Scheme 1, the synthesis of (*R<sub>P</sub>*)-**1** in good diastereomeric purity is challenging due to the fact that this compound is an oil at room temperature. Furthermore, all approaches employ P-Cl reagents, diethyl ether or THF as solvents, and cryogenic conditions during synthesis and/or purification. However, in spite of these practical issues, the reactions summarized in Scheme 1 have been conducted to prepare (*R<sub>P</sub>*)-**1** in large quantity (*ca.* 50 g or 0.18 mol). Because the vast majority of *P*-stereogenic phosphine ligands contain a phenyl group, *H*-phosphinate **1** has been extensively employed as starting material, and numerous highly stereoselective/stereospecific reactions have been described.<sup>5c,7,9</sup> Nonetheless, the ready availability of **1** remains questionable, let alone that of other menthyl *H*-phosphinates.

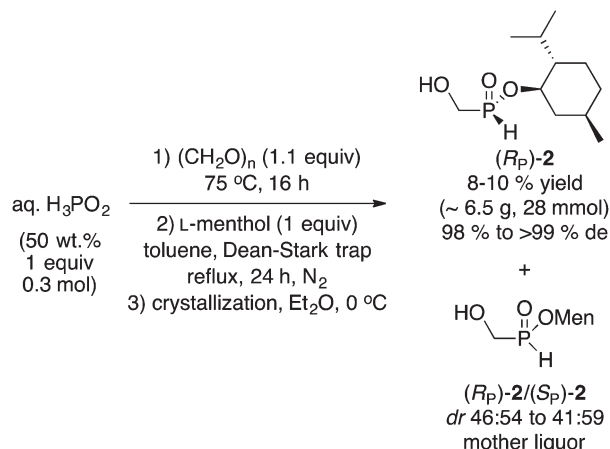
We recently communicated what we believe to be a general solution to the problem of preparing a variety of menthyl phosphinates (including **1**).<sup>10</sup> Herein, the full account of this work is presented.

## Results and discussion

Our methodology relies on two key discoveries: (1) the simple preparation of easily crystallized (hydroxymethyl)phosphinates,<sup>10</sup> and (2) the stereoselective cleavage of the hydroxymethyl moiety using the Corey-Kim oxidation to unmask a P(O)H moiety, if desired.<sup>10,11</sup> Of course, the hydroxymethyl methylene carbon can be preserved instead.

### Menthyl(hydroxymethyl)phosphinates

(Hydroxymethyl)-*H*-phosphinate **2** is the simplest member of this class of compounds.<sup>12</sup> The preparation of **2** is straightforward, as shown in Scheme 2. Heating commercially available aqueous hypophosphorous acid with paraformaldehyde, followed by azeotropic distillation with menthol in toluene afforded **2** as a 1 : 1 mixture of diastereoisomers. In our initial report,<sup>10</sup> the mixture was crystallized from ether at -18 °C in a standard freezer, however crystallization in a refrigerator at ~0 °C gave similar results, thus recrystallization from Et<sub>2</sub>O at 0 °C gave (*R<sub>P</sub>*)-**2** in 10% yield and >99% de. The absolute configuration was assigned *via* single X-ray crystallography.<sup>10</sup> Whereas the overall yield of (*R<sub>P</sub>*)-**2** is admittedly low, the process is very simple and does not require anhydrous conditions, base, organometallic reagent (Grignard or MenONa), nor cryogenic multiple recrystallizations. (Hydroxymethyl)-*H*-phosphinate (*R<sub>P</sub>*)-**2** is also ideal for further elaboration of the remaining P(O)H

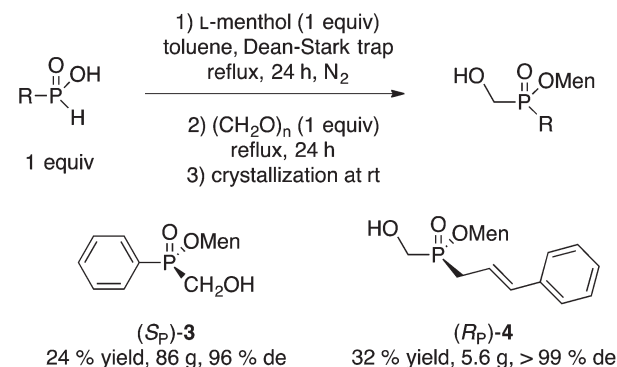


Scheme 2 Synthesis of (hydroxymethyl)-*H*-phosphinate (*R<sub>P</sub>*)-**2**.<sup>10</sup>

functionality. The leftover mother liquor can also be exploited further to increase its value (*vide infra*). Replacing (-)-menthol with (+)-fenchyl alcohol and (-)-borneol gave the corresponding esters in 3% yield (92% de), and 17% yield (88% de), respectively (the absolute configuration at phosphorus was not established in those cases since menthol was superior and is one of the cheapest chiral auxiliaries).

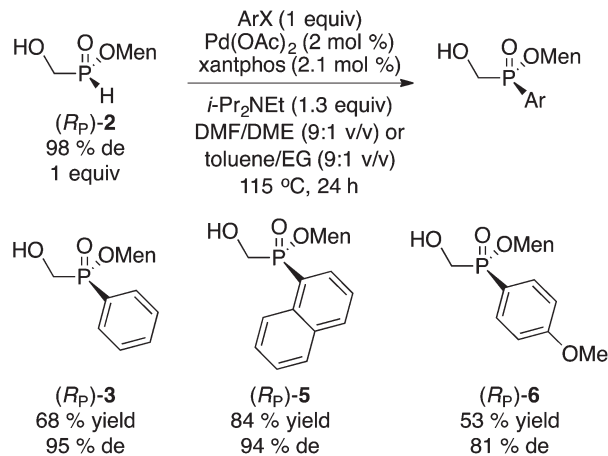
A similar direct esterification approach is also successful with some *H*-phosphinic acids RPO<sub>2</sub>H<sub>2</sub> (R = Ph, cinnamyl) as shown in Scheme 3.<sup>10</sup> However, the steps must be reversed (menthol then paraformaldehyde) because only *H*-phosphinic acids can be esterified under Dean-Stark conditions. Menthyl(hydroxymethyl)phenylphosphinate (*S<sub>P</sub>*)-**3** was obtained in 24% yield and 96% de after recrystallization at room temperature (similar results were obtained on a quarter scale).<sup>12</sup> The absolute configuration of (*S<sub>P</sub>*)-**3** was established by X-ray crystallography.<sup>10</sup> Cinnamyl-*H*-phosphinic acid gave (*R<sub>P</sub>*)-**4** in 32% yield and outstanding de.

In spite of the crystallinity typically displayed by (hydroxymethyl)phosphinates, the direct approach (Scheme 3) is not general and failed to provide an easily separable diastereoisomer with R = Me<sub>2</sub>C=CHCH<sub>2</sub>, Ph<sub>3</sub>C, *t*-Bu, CH<sub>2</sub>OAc, CH<sub>2</sub>OBn, MeC(OEt)<sub>2</sub> and Me<sub>2</sub>C(OH). Fortunately, (*R<sub>P</sub>*)-**2** can be employed as a general starting material to access numerous di-



Scheme 3 Direct reaction of *H*-phosphinic acids.<sup>10</sup>



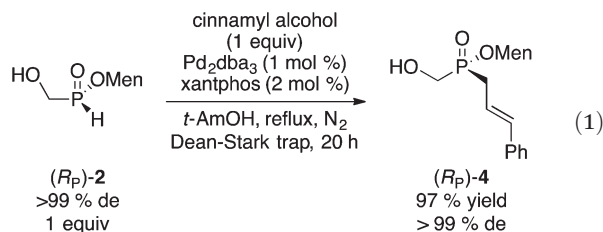
Scheme 4 Palladium-catalyzed cross-couplings of (*R<sub>P</sub>*)-2.

substituted menthyl(hydroxymethyl)phosphinates through various reactions. Scheme 4 summarizes some palladium-catalyzed cross-coupling reactions.

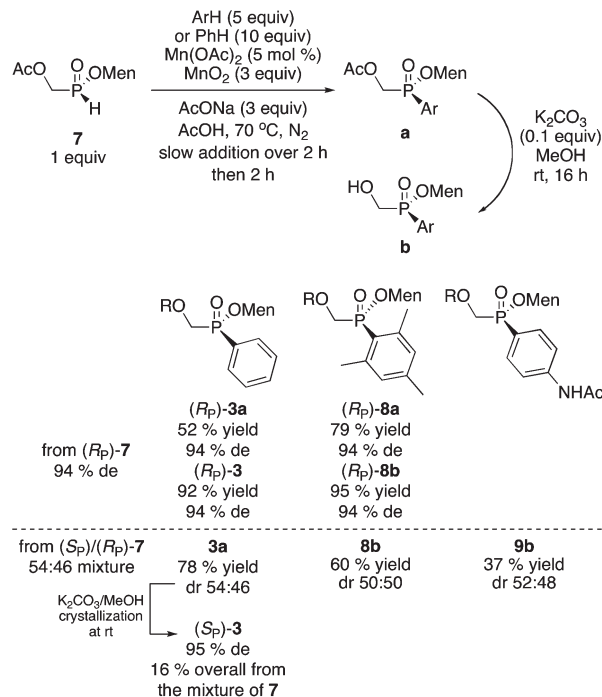
Interestingly, the cross-coupling of (*R<sub>P</sub>*)-2 with bromobenzene under conditions we previously developed<sup>13</sup> (Scheme 4), resulted in the formation of (*R<sub>P</sub>*)-3 through expected retention of configuration, thereby delivering the opposite configuration at phosphorus when compared to that of the direct approach in Scheme 3. However, the cross-coupling reaction sometimes resulted in some erosion in the de as shown with *p*-anisyl (*R<sub>P</sub>*)-6. Nonetheless, the Pd-catalyzed coupling<sup>13</sup> could be utilized to exploit the mother liquor leftover from the synthesis of (*R<sub>P</sub>*)-2. When a diastereomeric mixture of 2 ((*S<sub>P</sub>*)/(*R<sub>P</sub>*) 59:41) was reacted as in Scheme 4, room temperature crystallization of the crude product resulted in the formation of (*S<sub>P</sub>*)-3 in 23% yield (overall from H<sub>3</sub>PO<sub>2</sub>) and 97% de.<sup>10</sup>

We found that our palladium-catalyzed cross-coupling of allylic alcohols previously described with *H*-phosphinic acids<sup>14</sup> is also successful on *H*-phosphinate esters.<sup>15</sup> Thus, reaction of (*R<sub>P</sub>*)-2 with an equimolar amount of cinnamyl alcohol takes place smoothly to produce (*R<sub>P</sub>*)-4 in excellent yield and complete stereospecificity (eqn (1)).

Instead of the Pd-catalyzed cross-coupling, our Mn(II)-catalyzed/Mn(IV) promoted arylation<sup>16</sup> can be employed. In this case the hydroxyl group in 2 must first be protected as the acetate. Acetylation of (*R<sub>P</sub>*)-2 (or of the diastereomeric mixture of 2) proceeds stereospecifically and quantitatively (Ac<sub>2</sub>O, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C to rt, 20 h) to deliver acetate 7.



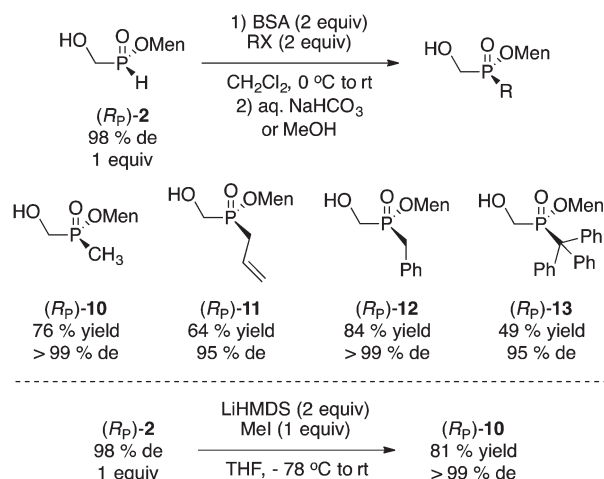
Acetate 7 was arylated as shown in Scheme 5. The reaction is stereospecific and proceeds with retention of configuration.



Scheme 5 Manganese catalyzed/promoted arylation.

Mesityl-substituted (*R<sub>P</sub>*)-8a was obtained in 79% yield without the need for a Grignard reagent. When 7 (obtained by acetylation of a mother liquor 2) was employed as starting material, compound 3a was obtained in 78% yield. Hydrolysis of 3a and crystallization at room temperature produces hydroxymethyl (*S<sub>P</sub>*)-3 in 16% overall yield (from the diastereomeric mixture of 7) and 95% de. Thus, although the yield is a little lower than in the Pd-catalyzed coupling we initially employed (23% yield, 97% de),<sup>10</sup> the present sequence is simpler and about ten times less costly.

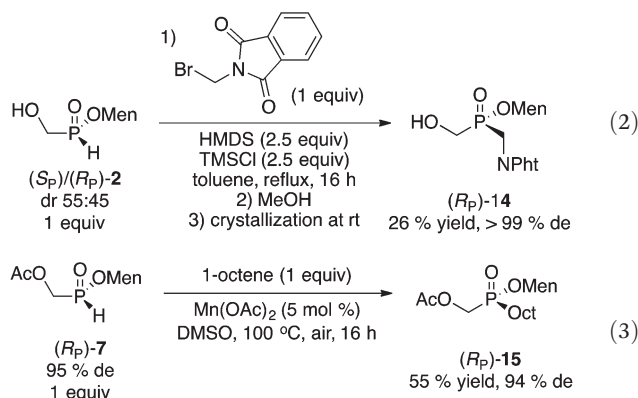
Next, the alkylation of (*R<sub>P</sub>*)-2 was examined and the results are summarized in Scheme 6. Sila-Arbusov alkylation<sup>17</sup> was

Scheme 6 Alkylation of (*R<sub>P</sub>*)-2.

conducted by mild silylation with *N,O*-bis(trimethylsilyl)acetamide (BSA, 2 equiv.) followed by addition of the electrophile (MeI, allylBr, BnBr, TrBr, 2 equiv.). Overall, good yields and diastereoselectivities were observed.

Whereas the yield of trityl **13** is moderate, this is quite remarkable and potentially useful to ultimately prepare extremely bulky phosphine ligands.<sup>18</sup> Early on, Mislow reported on the stereospecific (but condition-dependent) alkylation of (*R<sub>P</sub>*)-**1** with sodium hydride and methyl iodide.<sup>2b</sup> With (*R<sub>P</sub>*)-**2**, alkylation under basic conditions (LiHMDS) gave a good result with methyl iodide as the electrophile (Scheme 6),<sup>10</sup> but this was not investigated further considering the success and convenience of the sila-Arbuzov reaction.

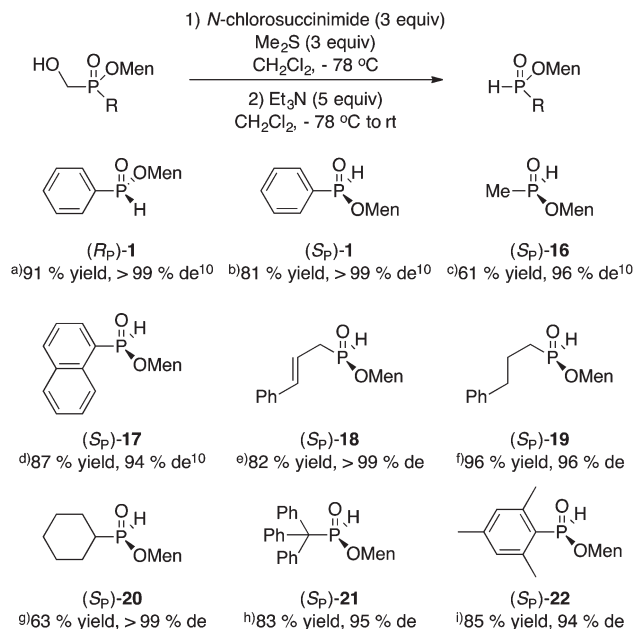
Finally, the reaction of unactivated (bromomethyl)phthalimide was examined using the more common silylation (HMDS/TMSCl)<sup>17</sup> from the diastereoisomeric mixture (mother liquor) of **2**. As shown in eqn (2), the overall yield was reasonable and the stereoselectivity excellent.



Next, we turned our attention to the free-radical reaction of 1-octene. Again, significant precedent exists with menthyl phenyl-*H*-phosphinate **1**.<sup>19</sup> However, aryl-*H*-phosphinates display special reactivities, because of their enhanced tautomerization properties.<sup>20</sup> Whereas compounds **2** and **7** should also be activated because of the electron-withdrawing nature of the hydroxymethyl moiety (PhCOOH  $pK_a = 4.18$ , HOCH<sub>2</sub>COOH  $pK_a = 3.83$ , AcOCH<sub>2</sub>COOH  $pK_a = 3.10$ ),<sup>21,22</sup> we chose conditions that should be generally applicable to any *H*-phosphinate ester. Therefore, our Mn(OAc)<sub>2</sub>-catalyzed reaction was examined (eqn (3)).<sup>23</sup> As with the arylation chemistry (Scheme 5),<sup>16</sup> protection of the hydroxyl as the acetate **7** was required. Product **15** was obtained in moderate yield but good diastereoselectivity.

### Menthyl *H*-phosphinates

The mild oxidative cleavage of disubstituted (hydroxymethyl) phosphinates was investigated next. We showed previously that Corey–Kim oxidation (*N*-chlorosuccinimide/Me<sub>2</sub>S) proceeds in good yield to unmask a P(O)H group from the P(O)CH<sub>2</sub>OH precursor.<sup>10,11</sup> Fortunately, this reaction is often stereospecific or at least highly stereoselective and proceeds in moderate to excellent yield. The results are shown in Scheme 7.



**Scheme 7** Synthesis of menthyl *H*-phosphinates. Configuration and de of the starting material: (a) (*S<sub>P</sub>*), >99%. (b) (*R<sub>P</sub>*), 95%. (c) (*R<sub>P</sub>*), >99%. (d) (*R<sub>P</sub>*), 94%. (e) (*R<sub>P</sub>*), >99%. (f) (*R<sub>P</sub>*), 98%. (g) (*R<sub>P</sub>*), >99%. (h) (*R<sub>P</sub>*), 95%. (i) (*R<sub>P</sub>*), 94%.

Additionally, the oxidation can be conducted with odorless and recyclable dodecyl methyl sulfide.<sup>24</sup> For example, the large scale (10 g, 32 mmol, >99% de) oxidation of (*S<sub>P</sub>*)-**3** delivered (*R<sub>P</sub>*)-**1** in 65% yield and >99% de. The long-chain sulfide was easily recovered quantitatively during purification and reused in other oxidations. An advantage of the Corey–Kim oxidation is that the sulfide can be used again directly without any intervening step, unlike oxidations involving the sulfoxide (Swern).

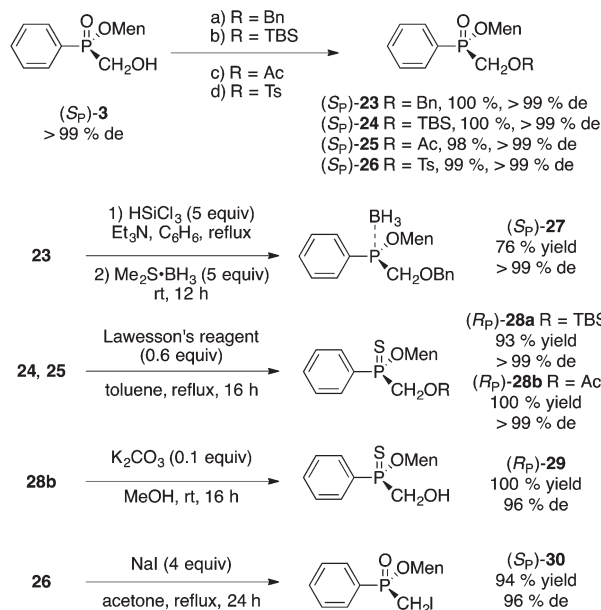
Our approach can deliver either absolute configuration at phosphorus, depending on the starting material that is chosen: (*S<sub>P</sub>*)-**3** (Scheme 3) delivers (*R<sub>P</sub>*)-**1**, whereas (*R<sub>P</sub>*)-**3** (Schemes 4 and 5) delivers (*S<sub>P</sub>*)-**1**. The preparation of (*S<sub>P</sub>*)-**1** via the literature procedures shown in Scheme 1 would require the use of D-(+)-menthol,<sup>7k</sup> which is about fifty times more expensive than L-(-)-menthol. If the ultimate goal is the preparation of a *P*-stereogenic tertiary phosphine, this does not matter since tertiary phosphine oxides can be reduced either with inversion or retention depending on the method employed.<sup>5d,w,25</sup>

On the other hand, the availability of either configuration of **1** using the same inexpensive L-(-)-menthol auxiliary could be an advantage for other applications, such as the synthesis of secondary phosphine oxide ligands.

### Reactions preserving the methylene carbon in menthyl (hydroxymethyl)phosphinates

As mentioned earlier, one advantage of our hydroxymethyl route<sup>11</sup> is that the carbon initially derived from formaldehyde can also be incorporated into *P*-stereogenic phosphinates. In



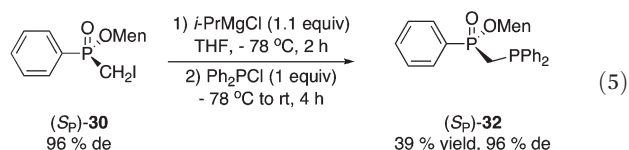
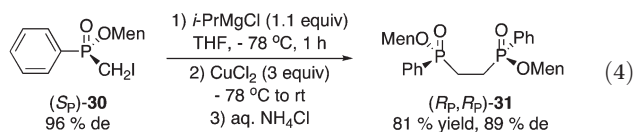


**Scheme 8** Modifications of (*S<sub>P</sub>*)-3. (a) NaH (1.5 equiv.), BnBr (1.2 equiv.), CH<sub>2</sub>Cl<sub>2</sub>, 0 °C to rt, 4 h. (b) *t*-BuMe<sub>2</sub>SiCl (1.5 equiv.), imidazole (2.7 equiv.), CH<sub>2</sub>Cl<sub>2</sub>, 0 °C to rt, 16 h. (c) Ac<sub>2</sub>O (1.2 equiv.), Et<sub>3</sub>N (1.25 equiv.), CH<sub>2</sub>Cl<sub>2</sub>, 0 °C to rt, 16 h. (d) TsCl (2 equiv.), *i*-Pr<sub>2</sub>NEt (2.5 equiv.), CH<sub>2</sub>Cl<sub>2</sub>, 0 °C to rt, 20 h.

the communication, we reported the Mitsunobu reaction of (*S<sub>P</sub>*)-3 with phthalimide (70% yield) and the Wittig rearrangement of allylated (*S<sub>P</sub>*)-3 in good yields and excellent stereoselectivity.

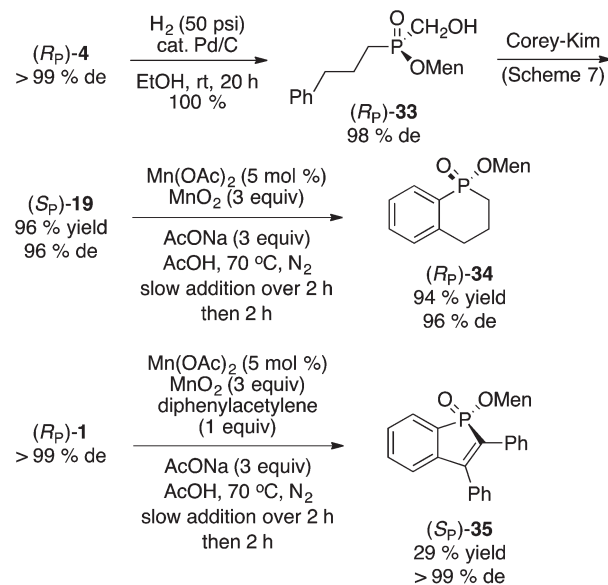
Standard reactions of the alcohol moiety (Scheme 8) in (*S<sub>P</sub>*)-3 took place uneventfully. Elaboration of the products could also be conducted to prepare phosphinite–borane complex 27, thiophosphinates 28 and 29, and iodide 30 (Scheme 8).

Magnesium–iodine exchange<sup>26</sup> of 30 gave a Grignard reagent, which was dimerized to afford bisphosphinate 31 (eqn (4)) or reacted with chlorodiphenylphosphine to produce 1,1-bisphosphorus compound 32 in low yield (eqn (5)).



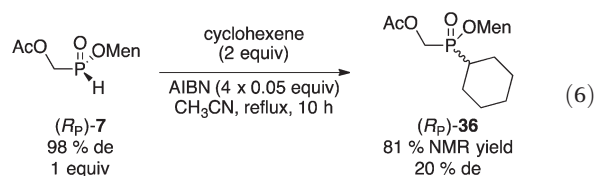
### Miscellaneous reactions

Scheme 9 shows the formation of two phosphinate heterocycles. Hydrogenation of cinnamyl phosphinate (*R<sub>P</sub>*)-4 to 33, followed by oxidation<sup>11</sup> gave (*S<sub>P</sub>*)-19 in excellent overall yield and good diastereoselectivity. Intramolecular Mn(II)/Mn(IV)



**Scheme 9** Formation of menthyl phosphinate heterocycles.

arylation<sup>16,23</sup> of (*S<sub>P</sub>*)-19 provided phosphinate 34 stereospecifically and in outstanding yield. On the other hand, annulation of (*R<sub>P</sub>*)-1 with diphenylacetylene under the same conditions delivered phosphinate 35 stereospecifically but in low yield (29%). It should be noted that this type of annulation has been described by Chen and Duan, with (*R<sub>P</sub>*)-1 (98% de) and diphenylacetylene but using Ag<sub>2</sub>O (2 equiv., DMF, 100 °C, 8 h) to produce 35 in a higher 40% yield, but with almost complete epimerization at the phosphorus center (26% de).<sup>27</sup>

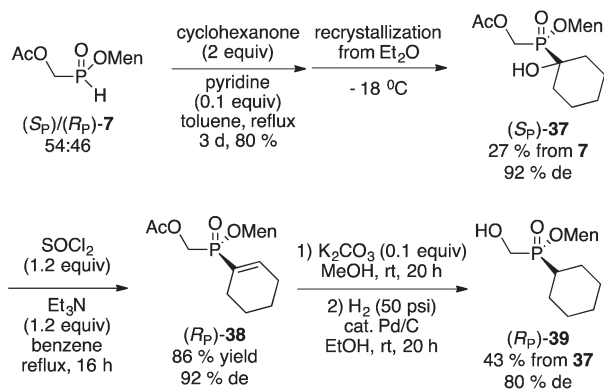


Next, we investigated the preparation of menthyl cyclohexyl-*H*-phosphinate 20 since cyclohexyl-substituted phosphines are bulky and electron rich, and popular in catalysis. The AIBN-initiated free radical addition of (*R<sub>P</sub>*)-2 or (*R<sub>P</sub>*)-7 to cyclohexene was unsatisfactory. As shown in eqn (6), almost complete epimerization (20% de) took place and so 36 was not isolated. The observed NMR yield does however support the unusual reactivity of 7 over other less electron-deficient *H*-phosphinates.<sup>20</sup> It is interesting to note that Han and coworkers reported the radical addition of (*R<sub>P</sub>*)-1 to be stereospecific.<sup>19</sup>

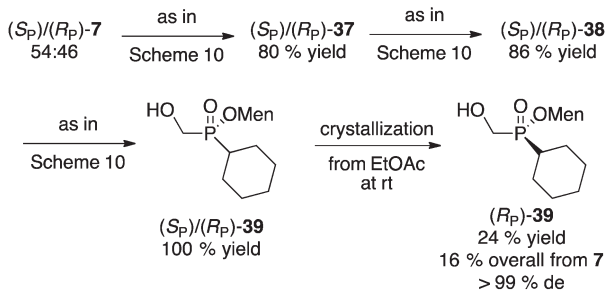
Initially, a circuitous route to the desired compound was devised starting from the mixture of diastereoisomers 7 (Scheme 10). Unfortunately, although intermediate 37 could be easily crystallized in acceptable diastereoselectivity, further erosion in diastereomeric excesses ultimately resulted in the production of 39 in low overall yield and poor 80% de.

Instead of separating the diastereoisomers early in the synthesis on cyclohexanone-adduct 37 (Scheme 10), postponing





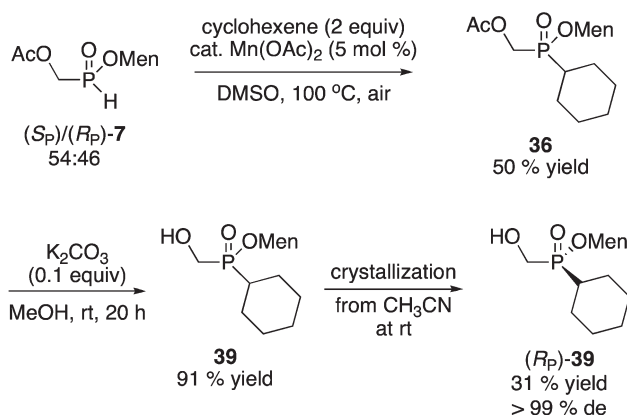
**Scheme 10** Alternate route to menthyl cyclohexyl-(hydroxymethyl)-phosphinate **39**.



**Scheme 11** Synthesis of  $(R_P)$ -**39** via late separation of the diastereoisomers.

this key step to the final product gave a much better outcome (Scheme 11). Thus, the mixture of **39** obtained from the mixture of **7** was easily crystallized to furnish  $(R_P)$ -**39** in excellent diastereomeric purity and acceptable overall yield.

Alternatively, the  $\text{Mn}(\text{OAc})_2$ -catalyzed addition of *H*-phosphinates could be employed (Scheme 12).<sup>23</sup> Again, the mixture of acetate diastereoisomers **7** (from the acetylation of the mother liquor) was employed as the starting material as a way



**Scheme 12** Alternative route to  $(S_P)$ -**39**.

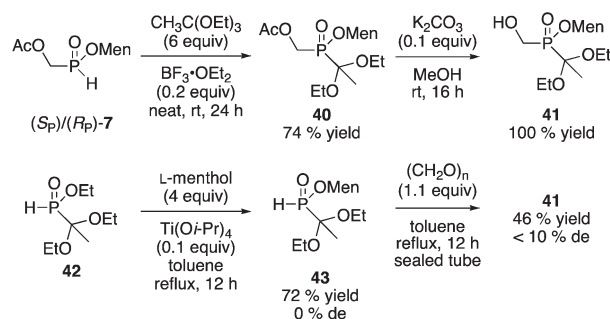
to further increase the value of the process shown in Scheme 2. Addition to cyclohexene proceeded in moderate yield (50%) to deliver **36**. Acetate hydrolysis under standard conditions produced **39** as a mixture of diastereoisomers, but crystallization then gave **39** in reasonable yield and excellent diastereoselectivity. In contrast, the Mn-catalyzed reaction<sup>23</sup> of  $(R_P)$ -**7** (96% de) with cyclohexene produced  $(R_P)$ -**39** in 90% de but only in 40% isolated yield.

Although it was not tried, in the final analysis the best route might be the AIBN-initiated addition of the mixture of diastereoisomers **7** to cyclohexene, followed by hydrolysis and crystallization as in Schemes 11 and 12. No matter the route, compound **39** can then be converted into menthyl cyclohexyl-*H*-phosphinate **20** as shown on Scheme 7.

The synthesis of other building blocks was investigated. Yokomatsu and coworkers investigated the preparation of *P*-stereogenic building blocks as precursors of phosphinyl dipeptide isosteres.<sup>28</sup> Their enzymatic resolution of the key ethyl 1,1-diethoxyethyl(hydroxymethyl)phosphinate ( $\text{MeC}(\text{OEt})_2\text{P}(\text{O})(\text{OEt})\text{CH}_2\text{OH}$ ) is important because in principle, the product could be elaborated into a variety of other organophosphorus compounds. However, the stereospecificity of the acetal cleavage was not established, and the resolution requires a 3.5:1 w/w ratio between enzyme (lipase AK) and substrate.<sup>28</sup> Nonetheless, the product could be obtained in 40% yield and 99% ee, with isoprenyl acetate as the reagent.<sup>28</sup>

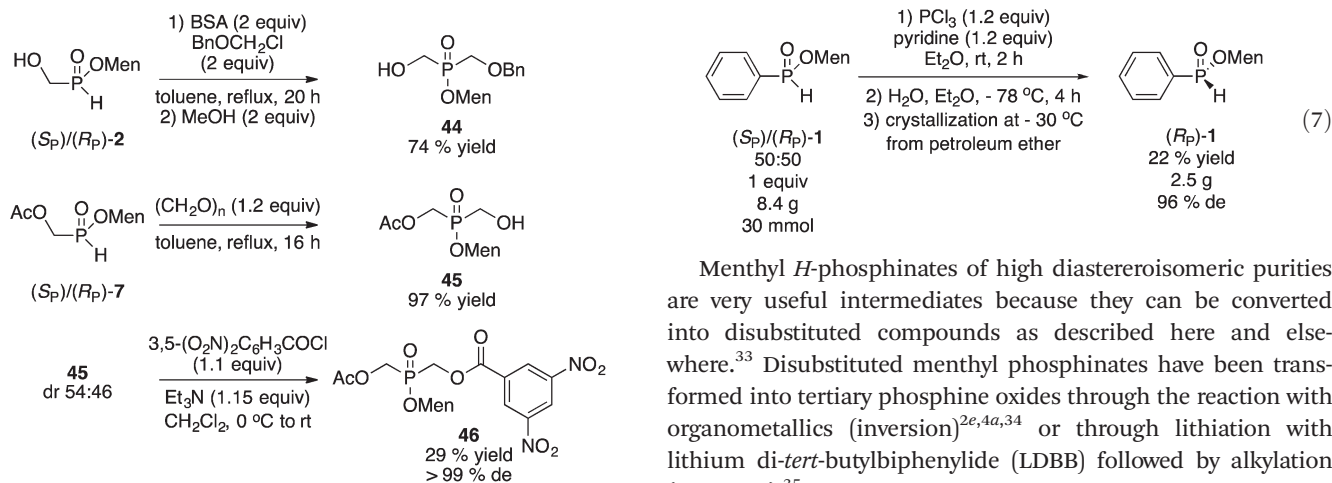
We decided to see if the menthyl phosphinate approach could be employed starting from the mixture of **2** or **7**. Protection of **7** using triethyl orthoacetate proceeded as we reported<sup>29</sup> to afford **40**, and subsequent hydrolysis gave **41** (Scheme 13). Unfortunately, neither **40** nor **41** could be crystallized to a pure diastereoisomer. Ciba-Geigy reagent **42**<sup>30</sup> could be transesterified ( $\text{Ti}(\text{O}i\text{-Pr})_4$ , menthol) to furnish menthyl(1,1-diethoxyethyl)-*H*-phosphinate **43**, but the diastereoisomers could not be separated by crystallization either.

Interestingly, the transesterification of *H*-phosphinate esters with menthol has not been described in the literature, though we have not yet investigated the generality of this process. Besides, one of our goals is to avoid the need to find crystallization conditions for numerous compounds, and instead to proceed from a handful of building blocks, especially **2** and **7**, as demonstrated in the present manuscript.



**Scheme 13** Attempted preparation of acetal-protected building blocks.





**Scheme 14** Differentially-substituted bis(hydroxymethyl)phosphinates.

Finally, the separation of differentially-substituted bis(hydroxymethyl)phosphinate derivatives was briefly examined (Scheme 14). Sila-Arbuzov alkylation<sup>17</sup> of **2** gave benzyl ether **44**. Alternatively, reaction of **7** with paraformaldehyde afforded acetate **45**. Neither product could be enriched by crystallization. However, reaction of **45** with 3,5-dinitrobenzoyl chloride gave the corresponding diester, which was easily crystallized from toluene at room temperature, to afford **46** as a single diastereoisomer (the absolute configuration at phosphorus has not been established) in 28% overall yield from the mother liquor **2**.

As mentioned in the introduction, numerous reactions have been described in the literature using (*R<sub>P</sub>*)-**1**,<sup>5c,7,31</sup> and few other menthyl *H*-phosphinates<sup>5c,9,32</sup> but to a much lesser extent. In our communication,<sup>10</sup> we also reported various reactions of (*R<sub>P</sub>*)-**1**, such as alkylation and cross-coupling. For example, menthyl methylphenylphosphinate (Knowles' intermediate in the synthesis of di-PAMP)<sup>4a</sup> was prepared through the sila-Arbuzov reaction as for (*R<sub>P</sub>*)-**2** in Scheme 6. Thus, (*R<sub>P</sub>*)-**1** (95% de) gave (*R<sub>P</sub>*)-menthyl methylphenylphosphinate in 90% yield and 94% de.

Having found that the hydrolysis of PhP(OMen)Cl can result in significant diastereoselectivity (see Scheme 1b), Han and coworkers reported the enrichment of (*R<sub>P</sub>*)/(*S<sub>P</sub>*)-**1** mixtures through chlorination with PCl<sub>3</sub> and subsequent hydrolysis.<sup>8</sup> Thus, a *ca.* 50 : 50 mixture of diastereoisomers **1** could be converted into an 88 : 12 mixture. In our case, the starting 50 : 50 mixture is an intermediate in the preparation of (*S<sub>P</sub>*)-**3** (Scheme 3), and surprisingly, this Dean–Stark synthesis of **1** (0% de) has not been reported previously, even though it can be conducted very easily on a large scale. Reaction of the mixture (8.4 g, 30 mmol) with PCl<sub>3</sub> and low temperature hydrolysis as described by Han, gave a 65% yield of a 82 : 18 diastereomeric mixture (64% de), which was crystallized from petroleum ether at –30 °C to afford (*R<sub>P</sub>*)-**1** in 22% overall isolated yield and 96% de (eqn (7)).

Menthyl *H*-phosphinates of high diastereoisomeric purities are very useful intermediates because they can be converted into disubstituted compounds as described here and elsewhere.<sup>33</sup> Disubstituted menthyl phosphinates have been transformed into tertiary phosphine oxides through the reaction with organometallics (inversion)<sup>2e,4a,34</sup> or through lithiation with lithium di-*tert*-butylbiphenylide (LDBB) followed by alkylation (retention).<sup>35</sup> Alternatively, Han showed that chlorination of menthyl-*H*-phosphinate esters with CuCl<sub>2</sub> or CCl<sub>4</sub> followed by substitution with Grignard reagents or other nucleophiles, takes place in excellent yields and stereoselectivities (inversion).<sup>36</sup>

Perhaps more importantly, the direct conversion of menthyl *H*-phosphinates into secondary phosphine oxides is well-established in the literature.<sup>7k,9,37</sup> The use of *H*-phosphinates has been limited mainly by the availability of the starting materials in good optical purity, a problem the present work has now largely solved (Scheme 7). Giordano and coworkers demonstrated the versatility of *P*-stereogenic adamantyl *H*-phosphinates RP(O)(OAd)H as “universal precursors of *P*-stereogenic compounds”.<sup>38</sup>

Borane complexes derived from menthyl phosphinates are another type of compounds whose popularity has been increasing.<sup>39</sup> Pietrusiewicz and Buono have devised methods to synthesize secondary phosphine–borane complexes from menthyl *H*-phosphinates.<sup>39a,b</sup> Early on, Imamoto prepared phosphinite–borane complexes<sup>39c–f</sup> from a different route (PhPCl<sub>2</sub>, RMgX, MenOH/Pyr, and separation by preparative thin layer chromatography) and showed that these products react stereospecifically (substitution with MeLi). Compound **27** (Scheme 8) is one example of a phosphinite–borane complex we synthesized in good yield and stereospecifically, but the scope of this reaction has not yet been examined. On the other hand, the direct borane reduction of disubstituted phosphinates possessing an unprotected hydroxyl group has been studied.<sup>40</sup>

## Conclusions

In spite of its historical importance, the use of *P*-stereogenic menthyl phosphinate esters has been hampered by their limited availability. Significant efforts have been devoted to the synthesis of *H*-phosphinates because of their synthetic flexibility: (1) displacement to secondary phosphine oxides, (2) functionalization to disubstituted menthyl phosphinates. Nonetheless, except perhaps for menthyl phenyl-*H*-phosphinate **1**, other *P*-stereogenic menthyl *H*-phosphinates have been elusive until now. Our methodology delivers versatile menthyl



(hydroxymethyl)-*H*-phosphinate ( $R_p$ )-2 in multigram quantities, through a very simple process that employs inexpensive reactants (aq.  $H_3PO_2$ , paraformaldehyde, and *L*-(-)-menthol) and straightforward crystallization. The reagent can be converted into numerous menthyl phosphinates through reactions like sila-Arbuzov alkylation, palladium-catalyzed cross-coupling, and manganese-catalyzed/promoted radical hydrophosphinylation/arylation. Furthermore, the mother liquor containing the mixture of diastereoisomers 2 can also be exploited to synthesize a variety of other valuable menthyl (hydroxymethyl)phosphinates through similar reactions. Corey–Kim oxidation of the hydroxymethyl intermediates affords the corresponding menthyl *H*-phosphinates in good yields and excellent stereoselectivities. Alternatively, the hydroxymethyl carbon can be incorporated into the products. The overall strategy avoids the need for chlorophosphines, Grignard reagents, strict anhydrous conditions, chiral HPLC separation, enzymatic resolution, cumbersome crystallization below  $-20\text{ }^\circ\text{C}$ , or expensive auxiliaries like ephedrine.

The present method offers practical and general synthesis of *P*-stereogenic menthyl phosphinates (including *H*-phosphinates), which have been established as important intermediates for the preparation of various *P*-stereogenic phosphine ligands. Thus, our approach constitutes a solution to the more than fifty year-old menthyl phosphinate problem of the asymmetric synthesis of *P*-stereogenic organophosphorus compounds.

## Experimental section

### ( $R_p$ )-Menthyl(hydroxymethyl)-*H*-phosphinate 2

Paraformaldehyde (9.91 g, 330 mmol, 1.1 equiv.) and hypophosphorous acid (39.6 g, 300 mmol, 1 equiv., 50% in water) were introduced in a round bottom flask and the reaction mixture was stirred for 24 h at  $75\text{ }^\circ\text{C}$ . The reaction mixture was cooled down to rt and the residue was diluted in toluene (300 mL). *L*-Menthol (46.9 g, 300 mmol, 1 equiv.) was added and the reaction mixture was stirred for 24 h at reflux under  $N_2$  in a flask equipped with a Dean–Stark trap. The solvent was then removed under vacuum and the residue obtained was dissolved in a mixture of diethyl ether/hexane (50 mL/200 mL) and the flask was placed in the refrigerator for 4 h ( $2\text{ }^\circ\text{C}$ ). The solid obtained was filtered and solubilized in diethyl ether (200 mL) and placed in the fridge ( $2\text{ }^\circ\text{C}$ ) for 3 h to afford the product as white needles (6.54 g, 10%, >99% de). Mp =  $101\text{--}102\text{ }^\circ\text{C}$ ;  $^{31}\text{P}$  NMR (162 MHz,  $CDCl_3$ ):  $\delta = 34.9$  (dm,  $J = 542$  Hz);  $^1\text{H}$  NMR (400 MHz,  $CDCl_3$ ):  $\delta = 7.16$  (dm,  $J = 542$  Hz, 1H), 4.04–4.23 (m, 2H), 3.82–4.00 (m, 2H), 2.14–2.24 (m, 1H), 1.98–2.11 (m, 1H), 2.04 (dq,  $J = 2.4$  and  $7.0$  Hz, 1H), 1.62–1.73 (m, 2H), 1.34–1.52 (m, 2H), 1.24 (q,  $J = 12.0$  Hz, 1H), 0.93 (d,  $J = 6.7$  Hz, 6H), 0.76–1.10 (m, 2H), 0.80 (d,  $J = 7.0$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz,  $CDCl_3$ ):  $\delta = 79.3$  (d,  $J_{\text{POC}} = 8.3$  Hz), 59.7 (d,  $J_{\text{PC}} = 111$  Hz), 48.5 (d,  $J_{\text{POCC}} = 5.5$  Hz), 43.3, 33.8, 31.5, 25.6, 22.9, 21.8, 20.8, 15.7; HRMS (ESI+)  $m/z$  calcd for  $C_{11}H_{23}O_3P$  ( $[M + Na]^+$ ) 257.1385, found 257.1423;  $[\alpha]_D^{22} = -61.4^\circ$  (chloroform).

### ( $S_p$ )-Menthyl(hydroxymethyl)phenylphosphinate 3

To a solution of phenylphosphinic acid (42.6 g, 300 mmol, 1 equiv.) in toluene (300 mL) was added *L*-menthol (46.9 g, 300 mmol, 1 equiv.). The reaction mixture was then stirred at reflux for 24 h under  $N_2$  in a flask equipped with a Dean–Stark trap. After cooling down the reaction to rt, paraformaldehyde (9.01 g, 300 mmol, 1 equiv.) was added and the reaction mixture was stirred at reflux for 24 h under  $N_2$ . The solvent was then removed under vacuum and the crude obtained was recrystallized at rt in diethyl ether (200 mL) to afford the product as colorless crystals (24.2 g, 26%, 97% de). Mp =  $138\text{--}139\text{ }^\circ\text{C}$ ;  $^{31}\text{P}$  NMR (162 MHz,  $CDCl_3$ ):  $\delta = 37.2$  (s);  $^1\text{H}$  NMR (400 MHz,  $CDCl_3$ ):  $\delta = 7.77\text{--}7.87$  (m, 2H), 7.52–7.60 (m, 1H), 7.42–7.51 (m, 2H), 4.29–4.43 (m, 2H), 3.93–4.10 (m, 2H), 2.26 (dq,  $J = 2.6$  and  $7.0$  Hz, 1H), 1.80–1.91 (m, 1H), 1.57–1.73 (m, 2H), 1.26–1.47 (m, 2H), 0.96 (d,  $J = 7.1$  Hz, 3H), 0.74–1.13 (m, 3H), 0.89 (d,  $J = 7.0$  Hz, 3H), 0.78 (d,  $J = 6.4$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz,  $CDCl_3$ ):  $\delta = 132.3$  (d,  $J_{\text{PCCC}} = 2.8$  Hz), 131.7 (d,  $J_{\text{PCC}} = 9.9$  Hz, 2C), 130.6 (d,  $J_{\text{PC}} = 123$  Hz), 128.3 (d,  $J_{\text{PCC}} = 12.1$  Hz, 2C), 77.1 (d,  $J_{\text{POC}} = 8.3$  Hz), 60.2 (d,  $J_{\text{PC}} = 117$  Hz), 48.7 (d,  $J_{\text{POCC}} = 6.1$  Hz), 43.2, 34.0, 31.4, 25.5, 22.8, 21.9, 21.1, 15.7; HRMS (EI+)  $m/z$  calcd for  $C_{16}H_{28}O_3P$  ( $[M + H]^+$ ) 311.1776, found 311.1766;  $[\alpha]_D^{22} = -46.7^\circ$  (chloroform).

### Representative procedure for the Corey–Kim oxidation.

#### ( $R_p$ )-Menthyl phenyl-*H*-phosphinate 1

To a solution of *N*-chlorosuccinimide (4.0 g, 30 mmol, 3 equiv.) in dichloromethane (150 mL) at  $-78\text{ }^\circ\text{C}$  and under  $N_2$  was added dropwise a solution of dimethyl sulfide (2.2 mL, 30 mmol, 3 equiv.) in dichloromethane (10 mL). After 30 minutes at  $-78\text{ }^\circ\text{C}$ , a solution of ( $S_p$ )-menthyl(hydroxymethyl)phenylphosphinate 3 (3.1 g, 10 mmol, 1 equiv.) in dichloromethane (30 mL) was added over 20 minutes. After 1 h at  $-78\text{ }^\circ\text{C}$ , triethylamine (7 mL, 50 mmol, 5 equiv.) was added over 15 minutes and the reaction was stirred for 30 minutes at  $-78\text{ }^\circ\text{C}$ . After warming up to rt, water was added and the two layers were separated. The aqueous layer was extracted with dichloromethane twice. The combined organic layer was dried over  $MgSO_4$ , filtered and concentrated under vacuum. The crude obtained was purified by column chromatography (hexane/ethyl acetate 9 : 1 to 8 : 2) to afford the product as a colorless oil (2.58 g, 92%, >99% de).  $^{31}\text{P}$  NMR (162 MHz,  $CDCl_3$ ):  $\delta = 24.7$  (dm,  $J = 553$  Hz);  $^1\text{H}$  NMR (400 MHz,  $CDCl_3$ ):  $\delta = 7.73\text{--}7.84$  (m, 2H), 7.66 (d,  $J = 553$  Hz, 1H), 7.46–7.64 (m, 3H), 4.22–4.36 (m, 1H), 2.14–2.27 (m, 2H), 1.62–1.75 (m, 2H), 1.38–1.54 (m, 2H), 1.24 (q,  $J = 11.2$  Hz, 1H), 0.78–1.13 (m, 2H), 0.96 (d,  $J = 7.0$  Hz, 3H), 0.90 (d,  $J = 6.4$  Hz, 3H), 0.86 (d,  $J = 7.0$  Hz, 3H);  $[\alpha]_D^{23} = -35.5^\circ$  (chloroform, literature with 90% de:  $-21.0^\circ$  in benzene).

## Author contributions

All authors have given approval to the final version of the manuscript.





## Competing interest

The authors declare no competing financial interest.

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